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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/582,916	10/02/2000	Carl Anthony Blau	UOFW115624	4343

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CHRISTENSEN, O'CONNOR, JOHNSON, KINDNESS, PLLC
1420 FIFTH AVENUE
SUITE 2800
SEATTLE, WA 98101-2347

EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/582,916	BLAU ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-88* is/are pending in the application.

4a) Of the above claim(s) *43,54,67-69 and 77-88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-42,44-53,55-66 and 70-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/17/04 has been entered. As requested, applicant's amendment and the declaration under 37 CFR 1.132 by Dr. Blau have been entered. Claims 1-88 are pending in the instant application. This application contains claims 43, 54, 67-69, and 77-88 drawn to an invention nonelected without traverse in Paper No. 12. Claims 1-42, 44-53, 55-66, and 70-76 are currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

Claim Rejections - 35 USC § 102

The rejection of claims 1-42, 44-53, 55-66, and 70-76 under 35 U.S.C. 102(e) as being anticipated over U.S. Patent No. 5,741,899 (4/21/98), hereafter referred to as Capon et al., is maintained. Applicant's arguments and the declaration by Dr. Blau under 37 CFR 1.132 have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

It is noted that the election of species by applicants of "hematopoietic stem cells", made without traverse in the response received on 8/30/02, still stands. The claims have only been examined to the extent that they read on the elected species.

The applicant argues that Capon et al. does not provide an enabling disclosure for making and using primary hematopoietic stem cells containing a construct encoding a fusion protein comprising at least one signaling domain and at least one drug-binding domain. The applicant provides three arguments in support of their position.

First, the applicant argues that constructs that contain multiple copies of an FKBP domain have a high frequency of rearrangement and that this would compromise the function of the introduced sequences, citing Thomis et al. (2001) Blood, 97(5), 1249-1257, page 1251, Col. 1. The declaration by Dr. Blau also states that at the time Capon et al. was filed, the only method for introducing genes into hematopoietic stem cells was retroviral transduction, citing Brenner et al. (1996) N.E.J.M. 335(5), 337-339, and that the inventor's group had shown that while electroporation of a vector encoding three copies of FKBP and the intracellular portion of c-kit can be used to achieve drug-induced proliferation of cells, retroviral injection of the same vector does not, citing Jin et al. (1998) Blood, 91(3), 890-897.

In response to the argument that the presence of 3 copies of the FKBP in a retroviral vector would result in rearrangement thereby inactivating the encoded fusion protein, please note that Thomis et al. was published in March 2001 and does not represent the state of the art at the time that Capon was filed in 1995. Further, Thomis does not provide any specific evidence that a retrovirus encoding 3 copies of FKBP would undergo rearrangement. On page 1251, Thomis states that they used codon-wobbled variants of FKBP in their retroviral vector in order to

decrease the risk or rearrangement. However, Thomis et al. does not demonstrate that in fact a retrovirus encoding 3 copies of FKBP would undergo rearrangement. Further, Thomis et al. states that rearrangement problems have not been reported previously in the literature (see Thomis et al., page 1251, column 1, 2 paragraph of the Results section). Thus, the evidence of record, including Thomis et al., does not establish that transduction of cells with a retroviral vector encoding 3 copies of FKBP would be ineffective in expressing the encoded fusion protein because of rearrangement.

Further, at the time that Capon et al. was filed, retroviral transduction was not the only method of introducing genes into hematopoietic stem cells. For instance, Musk et al. teaches successful gene transfer into human hematopoietic stem cells using DNA vectors and lipid transfection (Musk et al. (1995) J. Cell. Biochem., Suppl. 21A). Note as well that Brenner et al. does not teach that retroviral vectors are the ONLY vectors capable of gene transfer into hematopoietic cells. Brenner simply states that as of 1995, murine retroviral vectors were the only vectors known to unequivocally integrate DNA into cellular DNA (see Brenner, page 337, column 2). While Brenner teaches that integration is desired for persistent gene expression, clearly other types of vectors can be used, such as self-replicating vectors or even-short lived vectors (see Brenner, page 338, Figure 1). It is also noted that Capon et al., while exemplifying retroviral vectors, clearly teaches that other vectors such as DNA vectors can be used to introduce the CPRs into cells by electroporation, transfection or lipofection (Capon et al., column 19, lines 10-28). Thus, assuming for the sake of argument that a retrovirus encoding 3 copies of FKBP might undergo rearrangement, Capon et al. clearly teaches other viable alternatives to retroviral transduction.

Regarding Jin et al., the examiner cannot find any reference to the use of retroviral vectors in this publication. Jin et al. appears to teach only a plasmid vector. If the applicant has any further data regarding the use of retroviral vectors encoding FKBP that they wish to be considered by the office, it is suggested that they submit this data in a supplemental declaration. However, as discussed in detail above, the disclosure of Capon et al. is not limited to the use of retroviral vectors and clearly teaches the use of DNA vectors for introducing CPRs into cells.

As their second argument, the applicant states that Capon et al. describes in example 11 stimulating proliferation of cells genetically modified to express an FKBP containing fusion protein *in vitro* by culturing the cells in dishes coated with saturating concentrations of FK1012. According to the applicant, and the Blau declaration, saturating concentrations of FK1012 would not induce proliferation because by occupying all the FKBP sites, dimerization is prevented, citing Blau et al. (1997), Proc. Natl. Acad. Sci. U.S.A. Vol. 94, 3076-3081, at page 3078, Col. 1). However, the actual results presented in the Blau et al. publication refute this conclusion. Blau et al. on page 3078, Col. 1 states that at higher concentrations of FK1012, less proliferation is observed than at the optimal concentration which is 100nM. "Less proliferation" in this context, however, is still substantial. Figure 2 on page 3078 of Blau et al. provides a dose/proliferative response curve for cells transduced with the FKBP fusion proteins and treated with FK1012. At the highest concentrations, 1000 nM, proliferation is somewhat less than at 100 nM, but it is still substantially higher than baseline. Therefore, this argument is not compelling.

The third argument put forth by applicants is that Capon et al. does not teach reversibly inducing proliferation. The declaration and the applicant's argument cite a passage from Capon et al. which the applicants state demonstrates that Capon et al. did not contemplate the reversible

induction of cell proliferation. In response, please note that while the claims have been amended to recite, "wherein exposure of the transduced cells to the drug reversibly induces growth, proliferation or differentiation of the said cell", the claims do not contain any method steps wherein the proliferation of the cells induced by the drug is actually reversed. In the context of the claims, the added limitation of "reversibly" is a property of the drug, and is interpreted to mean that the effects of the drug are not permanent. Capon et al. clearly teach inducing proliferation by exposing transduced cells to FK1012. The effects of FK1012 in binding FKBP and inducing dimerization of the fusion proteins resulting in proliferation are inherently not permanent. This is evidenced by Blau et al., *supra*, which shows that FK1012 induction of proliferation in cells transduced with fusion proteins containing FKBP is reversible (Blau et al., page 3076, abstract).

Furthermore, applicant's quotation of the paragraph from Capon which deals with further including cytotoxic genes in the cells transduced to express CPRs does not demonstrate that Capon et al. did not contemplate that FK1012 induced proliferation would be reversible. In column 22, lines 2-19, Capon et al. is simply disclosing another embodiment of their invention. The disclosure of an additional embodiment does not negate the teachings of Capon et al. for simply transducing cells with the FKBP fusion protein alone. In addition, as noted above, the reversibility of the FK1012 induced proliferation is an inherent property of FK1012 as evidenced by Blau et al. Therefore, applicant's arguments are not found persuasive in overcoming the instant rejection of record.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER